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Neuroimaging in status epilepticus secondary to paraneoplastic autoimmune encephalitis

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AIM: To describe the characteristic magnetic resonance imaging (MRI) findings of paraneoplastic autoimmune encephalitis in patients with new-onset status epilepticus.

MATERIALS AND METHODS: The neuroimaging and clinical data of five patients with paraneoplastic autoimmune encephalitis debuting as status epilepticus were retrospectively reviewed. All patients met the criteria for definite paraneoplastic syndrome and all underwent brain MRI during the status epilepticus episode or immediately after recovery.

RESULTS: All patients showed hyperintense lesions on T2-weighted imaging (WI) involving the limbic structures, specifically the hippocampus. Three of them showed additional extra-limbic areas of signal abnormalities. The areas of T2 hyperintensity were related to the electroclinical onset of the seizures. In three patients, various techniques were used to study cerebral perfusion, such as arterial spin labelling MRI, single photon-emission computed tomography (SPECT) and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron-emission tomography (PET). Arterial spin labelling showed hyperperfusion overlapping the inflammatory lesions, whereas PET and SPECT disclosed increased perfusion and increased metabolism. The subtraction SPECT co-registered to MRI (SISCOM) demonstrated hypermetabolism outside the areas of encephalitis. After clinical recovery, follow-up MRI revealed the development of atrophy in the initially affected hippocampus. Two patients who had recurrent paraneoplastic autoimmune encephalitis manifesting as status epilepticus showed new T2 lesions involving different structures.

CONCLUSION: The presence of limbic and extra-limbic T2 signal abnormalities in new-onset status epilepticus should suggest the diagnosis of a paraneoplastic syndrome, especially when status epilepticus is refractory to treatment. The lesions are consistently seen as hyperintense on T2WI.

Introduction

Paraneoplastic autoimmune encephalitis (PE) is considered one of the classic paraneoplastic neurological syndromes (PNS), which are defined as neurological symptoms that are not associated with local or metastatic activity of a malignancy and sometimes supported by the presence of

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specific onconeural antibodies.[1] PE has been termed "limbic encephalitis", as it is often confined to the limbic system, especially the hippocampus and temporal cortex. However, some reports have described involvement of extra-limbic structures, such as the basal ganglia, mesencephalon, or neocortex, constituting the so-called "extra-limbic encephalitis".[2]

Despite relevant scientific advances, the pathophysiology of PE remains elusive. The diagnosis can be difficult because of the wide spectrum of clinical presentations of this condition. At onset, PE commonly appears as an insidious subacute cognitive-behavioural disorder, developing over a few days or up to 12 weeks.[3]

Seizures and epileptiform discharges have been described in nearly 29% of patients with PE.[4] However, convulsive status epilepticus (SE) is less commonly associated with PE.[2,5,6] Epilepsia partialis continua has been reported in 7% of patients with extra-limbic anti-Hu encephalitis.[4] Other types of SE are rare in PE, and cases of non-convulsive SE are often misdiagnosed as confusional states.[4,5]

PNS can be classified as "definite" or "possible" by combinations of a set of criteria[1] and both diagnoses require exclusion of other causes to explain the symptoms in a patient with malignant disease. The presence of well-characterized onconeural antibodies, even in the absence of a known tumour, can be used to classify the associated disorder as definite PNS.[1,3]

Magnetic resonance imaging (MRI) combined with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron-emission tomography (PET) and single photon-emission computed tomography (SPECT), are fundamental for detecting neurological complications of systemic cancer such as brain metastasis or carcinomatosis.[7] Although MRI findings are not considered diagnostic for PE and normal findings are not uncommon, the patients in the present study with SE secondary to PE showed abnormal MRI. Hypersignal on T2-weighted imaging (WI) involving various brain regions and indicating inflammation have been described and can support the clinical diagnosis, particularly in the absence of antibodies. Nonetheless, the rate at which these imaging abnormalities occur and their relationship with the clinical features of the condition are uncertain.[2] The aim of the present study was to describe the neuroimaging findings in patients with SE secondary to PE.

Materials and methods

The neuroimaging and clinical data of five consecutive patients admitted to Vall d'Hebrón University Hospital, Barcelona, Spain, with a diagnosis of SE secondary to PE between August 2005 and March 2011 were retrospectively reviewed. The study was approved by the hospital ethics committee.

All patients had seizures captured using video-EEG (electroencephalography) monitoring, and all underwent contrast-enhanced brain CT at hospital admittance, brain MRI, and determination of anti-neural antibodies (anti-Hu, anti-Ma2, anti-Yo, anti-CV2, anti-Ri, and anti-amphiphysin) in the cerebrospinal fluid (CSF).

Subsequent MRI was carried out within 6 months of SE using a 1.5 T magnet in three patients and a 3 T system in one patient. Whole-brain study with 5 mm section thickness was obtained by using (1) transverse T2WI; (2) transverse and coronal fluid-attenuated inversion recovery (FLAIR); (3) diffusion-weighted imaging (DWI) with b = 500 and 1000 s/mm^2; and (4) unenhanced and contrast-enhanced (0.1 mmol/kg body weight gadolinium-based contrast agent) transverse T1WI. A pulsed arterial spin labelling (ASL) sequence was also obtained during the 3 T imaging and was used to perform cerebral blood flow (CBF) mapping.

All patients underwent nuclear medicine examination to detect the underlying malignancy or to stage disseminated disease. Three patients were also studied using SPECT or PET to characterize the nature of the brain lesions. SPECT was obtained with 740 MBq of Tc-99m ethyl cysteinate dimer, using a double-headed gamma camera with high-resolution and low-energy parallel collimators. The FDG-PET examinations were performed with a three-dimensional mode in a single imaging session after injection of 2.5 MBq/kg of the radiotracer.

Results

Five patients with SE with definite criteria for PNS were reviewed. Four patients were men, and the mean age was 59 years. The existence of underlying cancer was identified with body PET/CT in three of the five patients at the onset of PE, and the two remaining patients were diagnosed during follow-up. Four lung cancers and one colon cancer were identified (Table 1).

At the time of the diagnosis, four patients were seen to have non-disseminated disease. Anti-Hu antibody was detected in the two patients with small cell lung carcinoma, which was discovered in one patient 4 years before the diagnosis of the primary tumour. In all cases, CSF analysis showed an inflammatory profile with high protein concentrations and low lymphocyte count.

In four patients, the clinical onset manifested as non-specific neuropsychiatric symptoms, such as mood lability, confusional state, and short-term memory impairment. The symptoms were insidious and had a waxing and waning course lasting from a few days to a month.

Behavioural disorders accompanied different types of epileptic seizures in all cases. SE was confirmed by clinical findings in two patients and by video-EEG in three patients with non-convulsive SE. Two patients had focal clonic seizures (cases 1 and 3). Three had autonomic seizures with diaphoresis, tachycardia, and piloerection (cases 2 and 3, and second episode case 4). Ictal speech arrest occurred in four patients (cases 2–5). One patient had convulsive SE that required sedation (case 4). Multiple anti-epileptic drugs were needed to decrease the seizures. A significant improvement in epileptic activity was only achieved when patients received treatment with gammaglobulin,